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RESEARCH ARTICLE

Neurological diagnoses in hospitalized COVID-19 patients during the B.1.1.529 surge

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Abstract

Objective: Emerging variants and sublineages of SARS-CoV-2 have differing disease severity, transmissibility, and immune evasion. The neurological conditions associated with the original strain of SARS-CoV-2 are well established. Our study assessed the neurological presentations specific to hospitalized patients during the B.1.1.529 (Omicron) variant surge in New York City. **Methods**: A total of 178 cases with positive RT-PCR result within 6 weeks before admission, and subsequent development of select neurological conditions during the SARS-CoV-2 B.1.1.529 (Omicron) surge between December 1, 2021 and February 28, 2022, were included from 12,800 SARS-CoV-2-positive hospital admissions. Clinical data from acute hospitalizations were compared to findings of inpatient neurological cases with COVID-19 infections from the initial surge in NYC in the same hospital system. **Results**: Compared to SARS-CoV-2 infections of the original strain, COVID-19 cases hospitalized during the Omicron surge (B.1.1.529) were associated with incidental and/or asymptomatic COVID-19 cases (96, 53.9%) and an increased incidence of pre-existing neurological and immunocompromising conditions. Encephalopathy, seizures, and stroke remained the most prevalent neurological conditions identified in hospitalized COVID-19 cases during the study period, reflecting a similar distribution of neurological presentations associated with the original strain. **Interpretation**: In our cohort of 178 admitted SARS-CoV-2-positive patients with select neurological conditions during the Omicron B.1.1.529 surge, 54% of COVID-19 cases were considered incidental and/or asymptomatic, and the identified neurological conditions resembled those associated with the original SARS-CoV-2 strain. Further studies characterizing neurological presentation in Omicron sublineages and other variants are warranted in an ongoing COVID-19 pandemic.

Introduction

The first case of SARS-CoV-2 variant B.1.1.529 (Omicron) was reported to the World Health Organization (WHO) on November 24, 2021, by the South African health authorities as a new variant of concern (VOC).[1–4] The Omicron VOC is the most divergent variant to date with a total of 65 mutations, 39 of which are located in the receptor-binding domain of the spike protein not detected in previous variants, concerning for potentially enhanced infectivity and immune evasion.[1,5–8] Lower mortality rates and less severe illness have been described in association with the Omicron B.1.1.529 variant compared to the preceding B.1.617.2 (Delta) variant and the original strain of SARS-COV-2, along with higher transmissibility, reduced neutralization by vaccine sera,

proliferation of sublineages, and increased risk for re-infection.[1–3,9–13] This potent combination has generated record surges worldwide, further perpetuated by additional Omicron subvariants including BA.2, BA.2.12.1, BA.4, BA.5, BQ.1, BQ.1.1, and XBB.1.5.[14–18] The speed with which each new Omicron subvariant emerges as the dominant strain and propagates vaccine breakthrough infections demonstrates an imperative to comprehensively detail the clinical features of each subvariant strain.

Neurologic involvement of COVID-19 infections manifests as a worsening of underlying neurological disorders, development of new neurological symptoms, or post-infectious sequelae.[19–21] While the acute neurological complications of those hospitalized with the original strain of SARS-CoV-2 have been extensively studied, few have explored the degree and variety of neurological presentations during the initial Omicron B.1.1.529 surge.[2,20–27] Our study aims to illustrate the spectrum of neurological manifestations, demographics, and clinical characteristics of hospitalized individuals during the SARS-CoV-2 Omicron B.1.1.529 variant surge in New York City (NYC).

Methods

Ethical clearance

This study received approval from CUIMC institutional review board (IRB) with a waiver of written informed consent for retrospective analysis.

Screening

We retrospectively reviewed the electronic medical records (EMR) of patients found to be SARS-CoV-2 positive by RT-PCR during or within 6 weeks of hospital admission date between December 1, 2021, and February 28, 2022, at Columbia University Irving Medical Center-New York-Presbyterian (CUIMC-NYP), Morgan Stanley Children's Hospital of New York (CHONY-NYP) and Allen Hospital (Allen-NYP) for inclusion in this study. Cases were defined as hospitalized patients who developed new neurological diagnoses within 6 weeks after a positive nasopharyngeal swab SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test result. Potential cases were identified from daily review of neurological admissions and CUIMC COVID-CARES database to include hospitalized patients with positive SARS-CoV-2 RT-PCR results admitted to CUIMC-NYP, CHONY-NYP, and Allen-NYP.[19]

Following the epidemiological curve of the Omicron B.1.1.529 surge in New York City, daily prospective review of potential cases began January 13, 2022, and ended February 28, 2022.[28] Additional cases were identified from the COVID-CARES database, an NYP hospital system wide database of all patients that were tested for COVID-19 in any NYP-affiliated outpatient and inpatient setting. Every 10th patient of 1986 SARS-CoV-2-positive patients admitted between December 1, 2021, and February 28, 2022, was reviewed for specified new neurological diagnoses to address selection bias for severe neurological conditions typically referred to neurological services. From 12,800 total hospital admissions during this period, 178 (1.4%) cases were included in this study: 107 cases from a prospective review of daily neurological service intake and 71 cases identified from a selective retrospective review of COVID-CARES (Fig. 1).

Analysis

Demographic and clinical data collected from EMRs were descriptively analyzed and compared to analogous data from the initial surge (March 1, 2020, to August 31, 2020) in NYC from the same institute. As reported by Thakur et al., the neurological cases were defined by the same inclusion criteria: diagnosis of select neurological conditions during the acute COVID-19 hospitalization within 6 weeks of a positive SARS-CoV-2 RT-PCR test.[19] This cohort of cases from the first SARS-CoV-2 surge during March – August 2020 will be referred to as group C. The cohort of cases identified during the study period corresponding with the first Omicron variant (B.1.1.529) surge during December 2021 – February 2022 will be referred to as group O.

Variables of interest included demographics, past medical history, COVID-19 vaccine status and treatment, intensive care unit (ICU) admission, and discharge status and location. Cases that were documented as asymptomatic by the primary care team, and incidental cases defined by non-COVID-19 related hospitalizations with RT-PCR positive results after admission, were identified. Risk factors pertinent to their neurological presentation were assessed for symptomatic patients. Chi-square test was applied to categorical variables, and two-sample t-test was applied to continuous variables in groups C and O.

Results

In our study, 178 group O cases from the Omicron B.1.1.529 surge with neurological diagnoses were included in the final analysis: 107 cases were identified from a prospective review of daily neurological service intake and 71 cases identified from a selective retrospective review of the COVID-CARES database during the study period (Fig. 1).[19]

The most common neurological diagnosis in group O was encephalopathy (122, 68.5%; $p = 0.027$) followed by

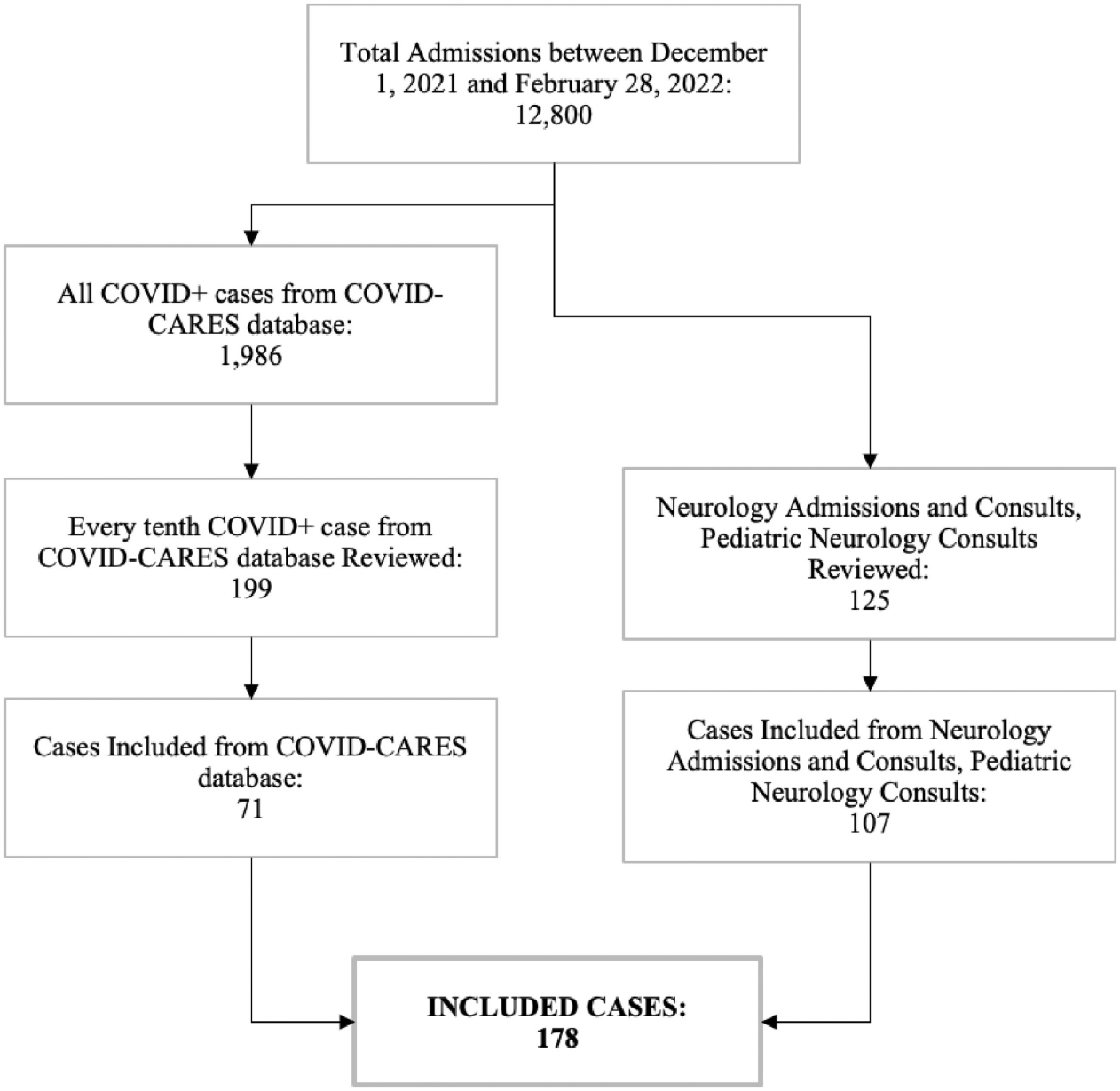

Figure 1. Workflow of screened cases.

seizure (45, 25.3%; $p < 0.001$), and ischemic stroke (37, 20.8%) (Table 1). There were no documented diagnoses of acute disseminated encephalomyelitis (ADEM), posterior reversible encephalopathy syndrome (PRES), or critical illness neuropathy. A higher frequency of encephalopathy (478, 89.8%) was observed in Group C while seizure (38, 7.1%) and stroke (66, 12.4%) were more prevalent in Group O.

Eighty-two (46.1%) cases were categorized as symptomatic SARS-CoV-2 infections in group O. Asymptomatic and incidental cases accounted for 53.9% (96) of all cases (Table 2). For group O cases requiring treatment for COVID-19 symptoms, 73 (41.0%) received anti-viral medication (remdesivir), 68 (38.2%) received steroids (dexamethasone), and 43 (24.2%) received both. Non-invasive ventilation was required in 61 (34.3%) patients from group O and 151 (28.4%) patients from group C. Invasive mechanical ventilation was required in 28 (15.7%) patients from group O compared to half of group C (278, 52.3%; $p < 0.001$). Among symptomatic COVID-19 group O cases, 77 (43.3%) had alternative etiologies for their neurological diagnoses due to multiple

Table 1. New neurological diagnoses of patients hospitalized during the Omicron B.1.1.529 variant surge compared to the first surge of COVID-19.

	March–August 2020 Group C		December 2021–February 2022 Group O		
Neurological diagnoses	*n*=	532	*n*=	178	*p*-value
Encephalopathy	478	89.8%	122	68.5%	0.027
Seizure	38	7.1%	45	25.3%	< 0.001
Ischemic stroke	66	12.4%	37	20.8%	0.001
Intracerebral/intracranial hemorrhage	33	6.2%	9	5.1%	
Encephalitis	0	0.0%	2	1.1%	
Guillain Barre Syndrome	0	0.0%	2	1.1%	
Meningoencephalitis	0	0.0%	2	1.1%	
Central nervous system (CNS) vasculitis	0	0.0%	1	0.6%	
Critical illness myopathy	19	3.6%	1	0.6%	
Meningitis	0	0.0%	1	0.6%	
Optic neuritis (ON)	0	0.0%	1	0.6%	
Acute disseminated encephalomyelitis (ADEM)	1	0.2%	0	0.0%	
Critical illness neuropathy	9	1.7%	0	0.0%	
Mononeuritis multiplex	1	0.2%	0	0.0%	
Multiple sclerosis (MS)	0	0.0%	0	0.0%	
Myelitis/myelopathy	1	0.2%	0	0.0%	
Narcolepsy/cataplexy	0	0.0%	0	0.0%	
Posterior reversible encephalopathy Syndrome (PRES)	3	0.6%	0	0.0%	
Meralgia paresthetica	1	0.2%	0	0.0%	
Other	0	0.0%	22	12.4%	

risk factors: diabetes mellitus (63, 35.4%), immunocompromised state (40, 22.5%), sepsis or bacteremia (21, 11.8%), and polysubstance abuse (15, 8.4%).

Sixty-five percent of patients in group O were vaccinated with at least one COVID-19 vaccination dose while 37 (20.8%) were not vaccinated, and the vaccination status of 26 (14.6%) patients was unknown. Unvaccinated cases were more prevalent in the symptomatic (22, 26.8%) than in the asymptomatic and/or incidental (15, 15.6%) subgroup (Table 3). Frequency of baseline neurological disorders was also similar between the subgroups. Symptomatic cases in group O had more males (46, 56.1%), ICU admissions (40, 48.8%), and deceased status (23, 28.0%) than those in group C. Notably, 81.7% of the symptomatic cases in group O were diagnosed with encephalopathy, proportionally similar to encephalopathic cases in group C (478, 89.8%).

The average (standard deviation) age of our group O hospitalized population was 58.6 (24.9) years with 50% > age 65 years compared to an older group C population (67.1 (17.8) years; $p < 0.001$) (Table 4). Ninety-two (51.7%) group O cases and 219 (41.2%) group C cases were male. Eighty-five (47.8%; $p < 0.001$) group O cases identified as non-Hispanic/Latino compared to 174 (32.7%; $p < 0.001$) group C cases. Eleven (6.2%) group O patients and 37 (7.0%) group C patients had no comorbidities.

Of the 167 (93.8%) group O patients with pre-existing medical conditions, the most common were hypertension (105, 59.0%), hyperlipidemia (55, 30.9%), and type 2 diabetes (52, 29.2%; $p = 0.04$) (Table 4). Similarly, hypertension (355, 66.7%), hyperlipidemia (176, 33.1%), and type 2 diabetes (151, 28.4%; $p = 0.04$) were most prevalent of the 495 (93.0%) group C patients with underlying disorders. One hundred and three (57.9%; $p < 0.001$) group O patients had underlying neurological disorders, of which the most common were seizure disorder (39, 21.9%), prior ischemic stroke (34, 19.1%), and Alzheimer's disease or other dementias (29, 16.3%). Significantly fewer (193, 36.3%; $p < 0.001$) group C patients had prior neurological conditions: 77 (14.5%) Alzheimer's disease or other dementias, 69 (13.0%) prior stroke, and 46 (8.6%) patients with seizure disorder. Group C patients also had lower rates of immunological disorders (63, 11.8%; $p < 0.001$).

Group O patients were hospitalized for an average of 20.5 days while 76 (42.7%; $p < 0.001$) patients were admitted to the ICU with an average ICU length of stay of 18.4 days. One hundred and forty-four (80.9%; $p = 0.078$) group O patients were discharged, while 33 (18.5%) patients died during hospitalization (Table 4). Group C cases had longer average hospitalizations (30.2 days), more ICU admissions (330, 62.0%; $p < 0.001$) with longer average ICU stays (26.0 days).

Discussion

As the Omicron B.1.1.529 variant and its sublineages drive the evolution of the COVID-19 pandemic into its fourth year, delineating the clinical profiles remains of critical importance. The Omicron B.1.1.529 variant of SARS-CoV-2 is distinguished from other VOCs by milder disease in all age groups with lower mortality compared to the original SARS-CoV-2 strain and other variants.[12,22,26,29,30] These features were observed by a record number of cases during the Omicron B.1.1.529 surge and the proportionally lower hospitalization and mortality rates.[31]

We found that more than half of the hospitalized cases with neurologic involvement in group O had asymptomatic and/or incidental COVID-19 infections. Given the majority of group O patients were at least partially vaccinated, SARS-CoV-2 RT-PCR positivity was found in 70

Table 2. COVID-19-related hospital data of patients with neurological diagnoses during first SARS-CoV-2 surge and Omicron B.1.1.529 variant surge.

	March 2020–August 2020 Group C		December 2021–February 2022 Group O		
	n=	532	*n*=	178	*p*-value
Vaccination status					
Vaccinated	0	0.00%	115	64.60%	
Partially vaccinated (1 mRNA dose)	0	0.00%	11	6.20%	
Completely vaccinated (2 mRNA doses/1 adenovirus dose)	0	0.00%	69	38.80%	
Boosted	0	0.00%	35	19.70%	
Unvaccinated	532	100.00%	37	20.80%	
Unknown	0	0.00%	26	14.60%	
COVID-19 infection					
Symptomatic	532	100.00%	82	46.10%	
Asymptomatic and/or incidental	–	–	96	53.90%	
Neurological risk factors	–	–	77	43.30%	
Diabetes mellitus	–	–	63	35.40%	
Immunocompromised state	–	–	40	22.50%	
Sepsis or bacteremia	–	–	21	11.80%	
Polysubstance abuse	–	–	15	8.40%	
COVID-19 treatment					
COVID-19 anti-viral medication (i.e., remdesivir)	29	5.50%	73	41.00%	
Steroids (i.e., dexamethasone)	220	41.40%	68	38.20%	
COVID-19 anti-viral medication and steroids	–	–	43	24.20%	
Oxygen supportive care					
Non-invasive ventilation	151	28.40%	61	34.30%	
Invasive mechanical ventilation	278	52.30%	28	15.70%	<0.001

Table 3. Asymptomatic and/or incidental compared to Symptomatic COVID-19 Cases during Omicron B.1.1.529 variant surge.

	Asymptomatic and/or incidental		Symptomatic	
	n = 96		*n = 82*	
Average age	58.8		56.3	
Sex				
Female	50	52.1%	36	43.9%
Male	46	47.9%	46	56.1%
COVID-19 vaccination status				
Vaccinated (at least one dose)	65	67.7%	50	61.0%
Not vaccinated	15	15.6%	22	26.8%
Unknown	16	16.7%	10	12.2%
Baseline conditions				
Neurological disorder	55	57.3%	48	58.5%
Immunological disorder	21	21.9%	21	25.6%
Neurological diagnosis				
Encephalopathy	57	59.4%	67	81.7%
Seizure	26	27.1%	21	25.6%
Stroke	25	26.0%	13	15.9%
Intracranial hemorrhage	3	3.1%	6	7.3%
ICU admission	37	38.5%	40	48.8%
Deceased	12	12.5%	23	28.0%

(39.3%) asymptomatic cases that did not require oxygen support or treatment with antivirals and steroids. With increased transmissibility and immune evasion, the Omicron B.1.1.529 variant has been implicated in a rise in incidental COVID-19 infections irrespective of vaccination status, particularly in prolonged hospitalizations and among transplant recipients by nosocomial transmission.[12,32,33] As vaccines were not yet authorized for emergency use during the first surge, none of the patients in group C were vaccinated and their primary cause of hospitalization was attributed to COVID-19.

During the initial outbreak, as outlined in Thakur et al., the most common new neurological diagnoses were encephalopathy (478, 89.8%), stroke (66, 12.4%), and seizures (38, 7.1%).[19] Neurologic involvement in group O was comparable to that of cases in group C, but there were proportionally more cases of seizure and stroke, and fewer encephalopathic cases in group O. This may be explained by a higher representation of pre-existing neurological disorders, specifically seizure disorder and risk factors for strokes, and immunologically compromised individuals in group O, primarily of malignancy and solid organ transplants. As more than 40% of group O had

Table 4. Demographic and clinical data of COVID-19 patients with neurological diagnoses during first SARS-CoV-2 surge and Omicron B.1.1529 variant surge in NYC.

	March – August 2020 Group C		December 2021 – February 2022 Group O		
	n=	532	*n*=	178	*p*-value
Demographics					
Age—average (SD)	67.1 years (17.8)		58.6 years (24.9)		<0.001
Age category	n	%	n	%	
1–17	15	2.80%	20	11.20%	
18–64	213	40.00%	69	38.80%	
65+	303	57.00%	89	50.00%	
Sex					0.095
Female	312	58.60%	86	48.30%	
Male	219	41.20%	92	51.70%	
Declined/unknown	1	0.20%	0	0.00%	
Race					0.441
White	141	26.50%	55	30.90%	
Black	112	21.10%	43	24.20%	
Asian	13	2.40%	2	1.10%	
Other/multiracial	154	28.90%	52	29.20%	
Declined/unknown	112	21.10%	26	14.60%	
Ethnicity					< 0.001
Hispanic/Latino	242	45.50%	70	39.30%	
Non-Hispanic/Latino	174	32.70%	85	47.80%	
Declined/unknown	116	21.80%	23	12.90%	
Past medical history					
	n=	*532*	*n*=	*178*	
None	37	7.00%	11	6.20%	
Pulmonary	96	18.00%	28	15.70%	0.559
Asthma	49	9.20%	8	4.50%	
Emphysema/chronic obstructive pulmonary disorder (COPD)	32	6.00%	11	6.20%	
Other	20	3.80%	12	6.70%	
Cardiovascular	383	72.00%	125	70.20%	0.47
Hypertension (HTN)	355	66.70%	105	59.00%	
Hyperlipidemia (HLD)	176	33.10%	55	30.90%	
Coronary artery disease (CAD)	75	14.10%	32	18.00%	
Heart failure/congestive heart failure (CHF)	43	8.10%	26	14.60%	
Atrial fibrillation	40	7.50%	27	15.20%	
Congenital heart disease	4	0.80%	2	1.10%	
Other	40	7.50%	25	14.00%	
Diabetes	232	43.60%	63	35.40%	0.04
Type 1	19	3.60%	3	1.70%	
Type 2	151	28.40%	52	29.20%	
Unspecified	62	11.70%	8	4.50%	
Neurological	193	36.30%	103	57.90%	< 0.001
Dementia/Alzheimer's disease	77	14.50%	29	16.30%	
Mild cognitive impairment	16	3.00%	2	1.10%	
Developmental delay	9	1.70%	7	3.90%	
Cerebral palsy	3	0.60%	4	2.20%	
Multiple sclerosis (MS)	1	0.20%	2	1.10%	
Seizure disorder	46	8.60%	39	21.90%	
Ischemic stroke	69	13.00%	34	19.10%	
Intracranial hemorrhage (ICH)	13	2.40%	5	2.80%	
Traumatic brain injury (TBI)	3	0.60%	0	0.00%	
Plegia/paralysis of other etiologies	7	1.30%	1	0.60%	
Other	13	2.40%	47	26.40%	
Immunological	63	11.80%	40	22.50%	< 0.001
HIV infection or AIDS (CD4 count <200)	10	1.90%	4	2.20%	
Solid organ transplant	13	2.40%	14	7.90%	
Cancer (current/in treatment or diagnosed in last 12 months)	39	7.30%	19	10.70%	
Other	0	0.00%	7	3.90%	
Clinical data					
Hospital length of stay (LOS)—average (SD)	30.2 days		20.5 days (24.6)		
Hospital LOS categorized	*n*=	*532*	*n*=	*178*	
0–3 days	60	11.30%	20	11.20%	
4–14 days	170	32.00%	86	48.30%	
15–30 days	105	19.70%	39	21.90%	
31–60 days	113	21.20%	18	10.10%	
61–100 days	64	12.00%	12	6.70%	
101+ days	19	3.60%	3	1.70%	
Intensive care unit (ICU) admission	330	62.00%	76	42.70%	< 0.001
ICU LOS—average (SD)	26.0 days		18.41 (42.28) days		
ICU LOS categorized	*n*=	*532*	*n*=	*178*	
1 day	13	2.40%	9	5.10%	
2–10 days	87	16.40%	34	19.10%	
11–30 days	116	21.80%	24	13.50%	
31–60 days	99	18.60%	6	3.40%	
60+ days	22	4.10%	3	1.70%	
Discharge status	*n*=	*532*	*n*=	*178*	0.078
Discharged	394	74.10%	144	80.90%	
Private home	–	0.00%	83	46.60%	
Rehab facility	–	0.00%	15	8.40%	

(*Continued*)

Table 4 Continued.

(*Continued*)

Table 4 Continued.

	March – August 2020 Group C		December 2021 – February 2022 Group O		
	n=	532	*n*=	178	*p*-value
Acute care facility	–	0.00%	2	1.10%	
Nursing home	–	0.00%	36	20.20%	
Hospice	31	5.80%	7	3.90%	
Deceased	138	25.90%	33	18.50%	
Readmission within 6 months	220/394	55.80%	–	0.00%	
Deceased on readmission	51/220	23.20%	–	0.00%	

neurological risk factors, an additional array of risk factors was potentially contributing to their neurological diagnoses, including diabetes, sepsis or bacteremia, polysubstance abuse, and immunocompromising condition.

Overall, group O cohort had reduced severity in COVID-19 infection, as evidenced by lower supplemental oxygen requirements, lower percentage of ICU admissions, shorter average hospital LOS and ICU LOS, and lower mortality, which is consistent with findings reported in numerous studies.[10,12,22,26,29,30,34] Mechanisms of lesser disease severity have been hypothesized: Viral infection limited to the upper respiratory tract and the inhibition of host cell interferon response have been proposed as mechanisms of lesser disease severity.[7] Neutralizing antibodies from vaccinations or prior infection confer protection against severe disease. Group O had a vaccination rate of 65%, which did not prevent their hospitalization but nearly 40% were admitted for medical concerns other than COVID-19 given their mild or absent COVID symptoms. The evidence of asymptomatic and/or incidental COVID-19 infection and alternative etiologies of neurological diagnoses renders an indeterminate association of neurological presentations with COVID-19 in group O.

To our knowledge, this is one of a few studies exploring the potential neurological complications associated with the Omicron B.1.1.529 variant. We were able to perform descriptive analyses between two cohorts of Omicron B.1.1.529 and original strain cases from the same institution with identical inclusion criteria and variables of interest, while further characterizing the asymptomatic and incidental COVID-19 infections of the Omicron cohort.

Limitations of this single site analysis include a small sample size of the Omicron cohort that is substantially vaccinated. Our Omicron cohort was also identified by an epidemiological curve for New York City outlined by the Department of Health due to unavailable sequencing data of patient specimens that would have provided verification of Omicron B.1.1.529 infection. Due to limited availability of medical record information regarding patient travel and social histories, we did not collect data for presumed time and place of acute and prior COVID-19 infection(s). With a significant portion of the Omicron cohort categorized as having incidental or asymptomatic COVID-19 disease, the neurological presentation that brought the patients in the Omicron cohort to the hospital cannot be associated with the B.1.1.529 variant.

As multiple Omicron sublineages rapidly displace and dominate prior strains resulting in overlapping surges and breakthrough infections in vaccinated populations, detailed clinical characteristics, including neurologic involvement, need to be established per variant and subvariant of concern. Distinguishing clinical profiles unique to specific strains may advance current knowledge of the evolution of SARS-CoV-2 mutations and its clinical implications.

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Author Contributions

CYK, JS, and KTT contributed to the conception and design of the study; CYK, ZS, BAA, SFD, CEB, YS, MC, HH, AB, and JZ contributed to the acquisition and analysis of data; CYK, ZS, BAA, SFD, CEB, JZ, RM, JS, and KTT contributed to drafting the text or preparing the figures.

Conflicts of Interest

JZ receives funding from NIH-NIAID; KTT receives funding from the Centers for Disease Control and Prevention (CDC) and the National Institute of Health (NIH), serves as an external consultant at the World Health Organization (WHO), Clinical Immunization Safety Assessment (CISA), CDC. The remaining authors report no disclosures.

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